



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/781,980	02/14/2001	Michael Eisenhut	41443	9550

35928 7590 04/22/2003

GRAY CARY WARE FREDENRICH
1625 MASSACHUSETTS AVENUE, NW
SUITE 300
WASHINGTON, DC 20036-2247

EXAMINER

SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
----------	--------------

1635

DATE MAILED: 04/22/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/781,980

Applicant(s)

EISENHUT ET AL.

Examiner

J. Douglas Schultz

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 February 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) 14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 and 15-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 February 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☒ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *See Continuation Sheet*.



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: ASSISTANT COMMISSIONER FOR PATENTS

Washington, D.C. 20231

Feb

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
---------------------------------	-------------	---	---------------------

EXAMINER

ART UNIT	PAPER
----------	-------

11

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. In the Office action dated August 13, 2002, applicants were notified that the instant application was not in sequence compliance. In a subsequent phone conversation with Dean Nakamura (see attached "Interview Summary"), Mr. Nakamura stated that their response to said Office action would include all documentation necessary to come into sequence compliance. However, no such documentation was received in said response, rendering a complete search of the instant application impossible. Furthermore, a subsequent phone message left with Mr. Nakamura's assistant regarding the failure of applicants' response dated February 13, 2003 to bring the application into sequence compliance has met with no response. Please see attached "Notice to Comply" for a listing of the required documentation.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

DETAILED ACTION

Applicant's response filed February 13, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed August 18, 2002 are hereby withdrawn. Applicants' amendment of claims 4-7, 9, 11, and 13-18 has been noted and fully entered. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Applicants amendments to the specification has been entered. However, applicants response fails to fully comply with the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Disclosures included in the previous Office action, because there is paper listing or Computer Readable Format has been received by the Office as of the time of the present time. Please see the attached Notice which reiterates the statement mailed with the previous Office action. Accordingly, claim 14, which is drawn to the oligonucleotide of SEQ ID NO: 1 has not been examined.

Response to Arguments

Claims 1-3 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nagy et al., in view of Lu et al. and Taylor et al, for the same reasons of record as set forth in the Office action mailed February 13, 2002.

Applicant has traversed the rejection above on the grounds that the presently claimed compositions comprising somatostatin analogs complexed to antisense oligonucleotides are larger than the compounds of Nagy et al., who teaches a somatostatin analog complexed to

Art Unit: 1635

doxorubicin. Applicant argues that Nagy supplies no expectation of success in using the larger size of the present compounds, because there is no expectation in Nagy that a molecule larger than doxorubicin could be internalized. Applicants also argue that one of ordinary skill in the art would expect that the size difference of the compounds in the instant complex, i.e. the large nucleotide and the relatively small somatostatin analog, would have a weakened affinity for each other because of said size difference. Applicant argues that passage of a nucleotide through the membrane is hard to predict. Applicant also argues that Lu et al., who teaches receptor-mediated uptake of antisense complexed to asialoglycoprotein, is not applicable because Lu only teach said uptake in normal cells, not cancerous cells as in the present invention; applicant argues that cancerous tissue is fundamentally different than normal tissues, and implies that said uptake wouldn't occur in cancerous tissue. Applicants allege that the complex of Lu is ionic, not covalent as presently claimed. Applicants argue that because Lu et al. reports significant success, that one of skill in the art would not be motivated to further modify the oligos of Lu. Finally applicant argues that Taylor et al. do not teach or suggest the instantly claimed complexes.

These arguments are not considered convincing. Regarding applicants' arguments that Nagy et al. do not provide an adequate expectation of success, it is pointed out that applicants later state that the success of Lu et al. is so strong that one of skill would not be motivated to further modify such complexes taught by Lu et al. This is obviously contradictory, since Lu and Nagy are used together in the instant obviousness rejection. The success of Lu et al. alone is sufficient to rebut applicants' argument; the complex of Lu is larger than applicants instant composition, and as noted by applicant, reports excellent results.

Art Unit: 1635

Applicants arguments that the instantly contemplated cancerous tissue is fundamentally different from the normal tissue used by Lu, and would teach away from using Lu in the method of Nagy is not adopted. One of ordinary skill in the art would recognize that cancerous tissue is different in that cells thereof replicate more, but otherwise act almost identically to normal cells. This is one reason cancerous tissue is so hard to target. Applicant has not provided any other reasoning or evidence as to why actively replicating cells (i.e. cancerous) would prevent the internalization of the compounds of Lu or Nagy. As an unsupported assertion, this is not convincing. Furthermore, applicants' assertion that the compound of Lu et al. is ionic is without support. Lu does not clearly indicate either way, but one can reason that since Lu indicates that the complex of asialoglycoprotein and oligonucleotide were dialyzed in an ionic solution which, if applicants allegation is true, would cause them to dissociate. It does not. The product was characterized further after this step.

Finally, applicants argue that Taylor et al. do not disclose the instantly claimed complex. Taylor et al. was relied upon only for the teaching that oligonucleotides can be modified to confer resistance to endogenous degradation, not to teach applicants whole invention. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Obviousness is not determined by what the individual references teach, but by what their combination as a whole would have suggested to one of ordinary skill in the art at the time of applicants' filing. As indicated above,

Art Unit: 1635

Applicants arguments are not considered convincing, and claims 1-3 stand rejected for the same reasons as set forth previously.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The above invention is drawn to methods of antisense therapy comprising the administration of pharmaceutical compounds comprising a complex of a somatostatin analog and an oligonucleotide. The claims of the above invention are also drawn to treatments of a host wherein said condition may be cancer, or any of a viral, inflammatory, asthmatic, central nervous system, or cardiovascular disease. The language of said claims encompasses *in vivo* activity. The specification teaches a method of making the claimed compositions, and also a method of determining the organ distribution that results from an injection of the claimed composition.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* is highly problematic. Thus, although the specification

Art Unit: 1635

prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in

Art Unit: 1635

predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch

Art Unit: 1635

affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of measuring the organ distribution that results from an injection of the claimed compound as being correlative or representative of the successful *in vivo* treatment using antisense compounds to treat any and/or all conditions or diseases suspected of being associated with protein expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or

Art Unit: 1635

preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

Said claims are drawn very broadly to methods of treating or preventing any condition or disease suspected of being associated with the expression of any protein in humans. Since the specification fails to provide any guidance for the successful treatment or prevention of such a broad range of diseases, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and /or tissues. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Claim 16 is drawn to a pharmaceutical preparation of applicants' claimed compound. Although the preparation of said compound is considered enabled, the specific reference to a pharmaceutical use in said claim constitutes functional language directed to *in vivo* use. Furthermore, it is applicants' intended *in vivo* use that forms the basis for the following

Art Unit: 1635

enablement rejection; for this reason, applicants' intended *in vivo* use of the compound of claim 16 necessitates its inclusion in this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagy et al. (of record), in view of Lu et al. (of record), Taylor et al. (of record), Anderson et al. (Chem Rev. 1999. 99:2219-2234), Khan, K et al. (J Chromat. Biomed. 702 (1-2) 69-76 (1997, Nov 21),

Art Unit: 1635

Godard, G et al. (Eur. J. Biochem. (1995 sep 1) 232 (2) 404-10), and Ma, D. D. F (Nucleic Acids Symposium Series (1998), 38: 175-176).

This rejection is similar to the obviousness rejection of the previous Office action, but is modified somewhat to address applicants' amended claims.

Claims 1-13 15, and 16 are directed to an oligonucleotide conjugate comprising an oligonucleotide complexed with a somatostatin analog wherein said oligo is complementary to a cellular mRNA transcript, wherein the oligonucleotide may be an oligodeoxyribonucleotide, or wherein the oligo phosphodiester bonds are at least partially replaced by phosphorothioate linkages, or wherein said oligo comprises a propanediol 3' end modification, or wherein said oligo contains an octreotide or octreotate somatostatin analog, or wherein said analog is covalently bonded to the 5' end, or wherein said analog is Tyr3 octreotate, or wherein said oligo targets mRNA or viral RNA or the coding region, or is 8 to 50 nucleotides long, or is 12 to 20 nucleotides long, or wherein said oligo targets bcl-2, or wherein said oligo is a peptide nucleic acid derivative.

Nagy et al. teaches highly bioactive somatostatin analogs that are conjugated to cytotoxic compounds, wherein said somatostatin analogs are used to deliver said cytotoxic compounds to cause cell death in cells that express somatostatin receptors (see abstract, page 1796 para. 4, and pg. 1796, last para, to 1797). Nagy et al. does not teach said analogs conjugated to an oligonucleotide, modified or otherwise.

Lu et al. teaches compounds that are complexed to an oligodeoxyribonucleotide that is antisense to cellular transcripts. The compound of the conjugates of Lu et al. are used to target cells expressing receptors that recognize said compound, thereby delivering the attached

oligodeoxyribonucleotide to specific cell types (see abstract, p. 273, para. 2, and discussion, particularly para. 1).

Ma, D. D. F teach bcl-2 antisense oligonucleotides conjugated to porphyrin to enhance targeting and cellular uptake.

Anderson et al. teach highly bioactive somatostatin analogs including octreotide, octreotate and Tyr3 Octreotate.

Taylor et al. teach that modification of antisense oligos, including the incorporation of phosphorothioate linkages into said oligos, confer a greater degree of resistance to nuclease-mediated-degradation (p. 562, para. 2 through p. 563), and pharmaceutical preparations. Taylor et al. also teach oligos that are modified at the base position, or that target mRNA or viral RNA or the coding region, wherein said oligos is 7-30 nucleotides long. Taylor et al. also teaches peptide nucleic acid (PNA) derivatives that are resistant to degradation.

Khan, K et al. teach 1-3 propanediol end modifications that confer nuclease resistance to oligonucleotides.

Godard, G et al. teach conjugates that are covalently bonded to the 5' position of oligonucleotides.

It would have been obvious for one of ordinary skill in the art to substitute either of the bcl-2 antisense from the conjugate of Ma et al. or the antisense compound of Lu et al. for the cytotoxic compound of the somatostatin analog conjugates as taught by Nagy et al. Furthermore, it would have been obvious to one of ordinary skill in the art to substitute the highly bioactive somatostatin analogs of Anderson et al. in place of the analogs of Nagy et al. It also would have been obvious to one of ordinary skill in the art to incorporate the nuclease resistance

modifications and targeting features of Taylor et al., Khan et al., and Godard et al. into such conjugates.

One would have been motivated to substitute the bcl-2 antisense from the antisense/porphyrin conjugate of Ma et al. or the antisense from the antisense/asialoglycoprotein conjugate of Lu et al. for the doxorubicin of the somatostatin-analog /doxorubicin conjugates as taught by Nagy et al., because Nagy et al. teach that somatostatin conjugates can be used to deliver cytotoxic compounds to target cells that express the somatostatin receptor, which is abundantly expressed on many cancer cell types, and because both Lu and Ma show that conjugates comprising oligonucleotides and a targeting compound can more effectively deliver said oligonucleotide to its target. One would have been motivated to use the somatostatin analog compounds of Anderson in such conjugates, because Nagy expressly teaches that such bioactive analogs of somatostatin can be used to deliver cytotoxic compounds, and because both Nagy and Anderson teach that such analogs have an increased half-life, which is desirable for longer bioactivity. Finally one would have been motivated to design such modifications into the instant oligonucleotide conjugates in the manner of Taylor et al., Khan et al., or Godard et al., because Taylor teach that oligos 7-30 nucleotides long are optimal for target access, that the coding region of mRNA's are preferred targeting sites. Taylor et al., and Khan et al., teach that phosphorothioate, base, PNA modifications, 1-3 propanediol modifications, improve bioactivity half-life and cellular uptake of antisense molecules, respectively. Godard et al., teaches 5' binding of conjugate to oligo, which comprises a design choice that was known in the art. One of ordinary skill in the art would have had a reasonable expectation of success in formulating such conjugates, because Nagy and Lu et al. teach their methods of synthesis, because bcl-2 antisense

Art Unit: 1635

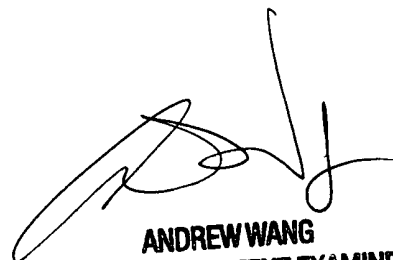
was known in the art via Ma, and because such design modifications are clearly described routinely performed by those of ordinary skill in the art. Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
April 18, 2003



ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600